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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,825	02/19/2002	Wolfgang M. Franz	0690-0115P	6306

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,825	FRANZ, WOLFGANG M.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2004* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-52* is/are pending in the application.

4a) Of the above claim(s) *47-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-46 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8/5/04* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/5/04 has been entered.

The response and amendment filed 8/5/04 has been entered. Claims 34-36 and 50 have been amended. Claims 51-52 are newly submitted, and claims 34-52 are pending in the application.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims and arguments will not be reiterated. The arguments in 8/5/04 response would be addressed to the extent that they apply to current rejection.

Restriction and Election

Applicants assert that claims 47-49 are improperly withdrawn from consideration because they depend from claims of the elected invention group, and they are not described as products of any method of transformation.

The argument has been fully considered but found not persuasive because first the restriction is determined by the nature of the claimed subject matter, not by claim dependency. Secondly, the elected invention is drawn to transfecting pluripotent stem cells with a cassette having promoters that only functions in either said stem cells or a cardiomyocyte. Thus, claiming any cell transfected with such expression cassette would lead to a different invention drawn to cells with different utility and require different search and technical consideration. Thirdly, since these claims are directed to an invention that is independent or distinct from the invention originally claimed for above reasons, they would have been restricted from instantly claimed invention if presented originally. Since applicant has received more than an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, it is proper that claims 47-49 be withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Applicants then argue that the present application is a National stage application of a PCT application, so the rules governing Unity of Invention govern restriction practice.

In response, the initial restriction was conducted according to this rule (See pages 2 and 3 of Paper No. 6), and has shown that the existing groups lack unity according to the International Preliminary Examination Report. Accordingly, the restriction is maintained, and is hereby made **final**.

With respect to claim 34, it was acknowledged in the previous Office action as generic, and only a species has been examined because it is considered as constructively elected by original presentation. It is also acknowledged that upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-46, and 50 stand rejected, and claims 51 and 52 are newly rejected under 35U.S.C. 112 first paragraph, because the specification as originally filed does not describe the invention as now claimed, for reasons of record and following.

In 8/5/05 response, applicants first argue that the general concept of an enhancer is mentioned at page 10 of the specification, whereas the CMV enhancer is mentioned at page 13 of the specification, thus the specification has the support for the claimed subject matter. Applicants also submitted exhibit 1 as evidence of the CMV enhancer function.

In response, it is noted the rejected new matter is not the general concept of an enhancer but the genus of enhancers operative in a mammalian embryonic stem cell and primordial cell, it is to this extend the new matter is introduced since the specification as originally filed discloses only individual enhancer and promoter such as a PGK promoter and a CMV enhancer. The specification is completely silent with respect to a genus of promoters that constitutively operabtive in a mammalian ES cell, primordial cell, or bone marrow stromal cell. Thus, simple mentioning of the CMV enhancer alone is not a support for the claimed genus because as indicated in the newly submitted Exhibit 1, the catalog page indicated that the CMV promoter/enhancer as one that allows strong constitutive expression in many cell types, and it is silent with respect to the CMV enhancer in an ES stem cell or a primordial cell, or a genus of enhancers operative in an ES cell or a primordial cell. Further, the catalog page only teaches how the CMV promoter/enhancer as one functions, and does not teach how the CMV enhancer functions when it is paired with a (any) cardiac muscle-specific promoter or a (any) constitutive promoter of a mammalian ES cell or primordial cell promoter, thus, neither the specification, nor the newly submitted exhibit support the broadly claimed genus.

Applicants then pointed to the last paragraph of page 10 to the first paragraph of page 11, the text at page 20, and figure 1 as the support for the genus of promoters constitutively operative in an ES cell or a primordial cell. Applicants further cited the Lallemand reference as support.

In response, it is noted that the last paragraph on page 10 discusses a selectable marker, not a promoter; the first paragraph of page 11, the text at page 20, and figure 1 only mentions the PGK promoter, not the genus of promoters constitutively operative in an ES cell or a primordial cell. Likewise, the *Lallemand* reference teaches a PGK-cre transgene, not the genus of promoters constitutively operative in an ES cell or a primordial cell or a BM stromal cell.

Applicants then pointed to claims 35 and 36 as drawn to individual promoter and enhancer, and thus should not be included in this rejection.

In response, claims 35-37 are included in this rejection because of another new matter, which applicants failed to response in the 8/5/04 Remarks, and which will be reiterated as following.

"the cassette claimed in claim 34 (D) or (E) differs from originally disclosed wherein the loxP flanks both the PGK promoter and the antibiotic resistance gene, thus, the amendment is a departure from or an addition to the disclosure of the application as filed. Accordingly, the amendment introduces new matter into the disclosure."

Currently, the claims read on the loxP only flanks the selectable marker gene but not the promoter constitutively operative in a mammalian ES or primodial cell or BM stromal cell. Figure 1 of the specification further evidenced such discrepancy.

Accordingly, it is maintained that the amended claims 34-46, 50, and newly submitted 51, 52 introduced new matter into the disclosure. Applicant is required to cancel the new matters in the reply to this Office Action.

For reasons set forth above, the amendment filed 2/20/04 stands objected to under 35 U.S.C. §132 because it introduces new matter into the disclosure. 35

U.S.C. §132 states that no amendment shall introduce new matter into the disclosure of the invention. Applicant is required to cancel the new matter in the reply to this Office Action.

To the extent that the claimed methods are not described in the instant disclosure, claims 34-46 and 50 stand rejected and claims 51, 52 are newly rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been adequately described, and that is not conventional in the art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 34 (A, B), 35, 38, 39, 40, 42, 46, and 50 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Klug et al* (J Clin Invest 1996;98:216-24), *Gaines et al* (IDS, Biotechniques 1999;26:683-8), *Griscelli et al* (Hum Gene Ther 1998;9:1919-28), and *Wolfgang-M et al* (J Mol Cell Cardiol 1997;29(5):A125), and in view of *Mack et al* (J

Thorac Cardiovasc Surg 1998;115:168-76), and the rejection now applies to claims 51 and 52, for reasons of record and following.

The combined teachings of *Klug et al, Gaines et al, Griscelli et al, Wolfgang-M et al, in view of Mack et al* are discussed in detail in the previous Office action.

New claims 51 and 52 define the electrophysiological properties of the cells produced by the method of claim 50, such properties are typical of cardiomyocytes as indicated in the specification (Specification, page 16, 3rd paragraph). Since *Klug et al* has taught generation of cardiomyocytes from differentiating ES cells, and success of using such cardiomyocytes for intracardiac transplantation, the cardiomyocytes taught by the combined teachings of *Klug et al, Gaines et al, Griscelli et al, Wolfgang-M et al, in view of Mack et al* would intrinsically possess the recited electrophysiological property in the absence of evidence to the contrary.

Accordingly, for reasons of record and those set forth *supra*, the combined teachings make obvious over the claimed invention.

Claims 34 (C-E), 36, 37, 41, 43-45 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Klug et al* (J Clin Invest 1996;98:216-24), *Gaines et al* (IDS, Biotechniques 1999;26:683-8), *Griscelli et al* (Hum Gene Ther 1998;9:1919-28), *Wolfgang-M et al* (J Mol Cell Cardiol 1997;29(5):A125), and *Mack et al* (J Thorac Cardiovasc Surg 1998;115:168-76) as applied to Claims 34 (A, B), 35, 38, 39, 40, 42, 46, and 50-52 above, and further in view of *Graham et al* (US 6,080,569), *Gainer et al*

(Transplant 1998;66:194-9), and *Lallemand et al* (Transgenic Res 1998;7:105-12), for reasons of record and set forth in the immediate preceding rejection.

Response to Arguments

In the 8/5/04 response, Applicants first argue that the cited references do not describe or suggest each and every limitation of the present claims, and at least the recitation of "at least one IRES operatively linked to at least one polynucleotide encoding an angiogenesis factor" is not described or suggested by any reference.

The argument has been fully considered but found not persuasive. This is because applicants argue against the references individually while the rejection is established on the combined teachings of the prior art. One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). As discussed above, the specific combination of IRES and angiogenic factor was taught by the combined teachings of *Klug et al, Gaines et al, Wolfgang-M et al, and Griscelli et al* in view of *Mack et al.* It appears that Applicants are arguing that the cited references do not expressly suggest the claimed invention. However, it is well established in case law that a reference must be considered not only for what it expressly teaches, but also for what it fairly suggests. In re Burkel, 201 USPQ 67 (CCPA 1979). Furthermore, in the determination of obviousness, the state of the art as well as the levels of skill of

those in the art are important factors to be considered. The teaching of the cited references must be viewed in light of these factors. In the instant case, at the time of instant effective filing date, it is well known in the art that the IRES could be built-in an expression cassette for coordinating expression of multiple heterologous genes simultaneously as taught by *Gaines et al*, and therapeutic cardiac genes such as angiogenesis factor VEGF could be used together with other cardiological procedure to improve the outcome of the myocardial function in patients with heart disease as taught by *Mack et al*, and generating pure population of cardiomyocytes from genetically manipulated ES cells for cardiac transplantation is also known in the art as taught by *Klug et al*, thus, it would have fairly suggested to the reasonably skilled in the art to include an IRES-VEGF in the ES cell manipulation construct with reasonable expectation of success.

Applicants then asserts that the motivation for combining the references is entirely lacking, and the rejection constitutes improper hindsight reconstruction. Specifically, applicants allege that the motivation to combine IRES with a polynucleotide encoding an angiogenesis factor is lacking, and the combined references fail to describe each element and arrange them in the manner described by the claims.

As an initial matter, it is noted applicants fails to point out which element has not been described by the combined teaching.

With respect to the motivation to combine IRES with a polynucleotide encoding an angiogenesis factor, as reiterated above, the motivation is clearly taught by *Gaines*

et al, who uses IRES for co-expression of multiple gene products, and clearly teaches using the IRES for coordination is advantages over co-transfected or dual-promoter vectors because the expression could be timely controlled (coupled, mid-column, page 1). Although the teaching is generic to any multiple gene-expression, not limited to angiogenic factors, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the combined teachings, particularly the teachings of *Gaines et al* and *Mack et al* would have suggested to those of ordinary skill in the art that IRES could be used to express angiogenesis factors along with other heterologous gene in treating cardiac ischemic disease when such is desired or necessary. Accordingly, the invention as a whole is obvious over the combined teaching of the prior art.

The arrangement of elements as claimed and the method of using such for differentiating ES cells to cardiomyocytes are generally laid out by the *Klug et al*, it is only the technical details drawn to a particular species of combination of promoters, enhancers that need supplementation by other prior art teaching to optimize the claimed cassette and method. Given the knowledge of skilled in the art with respect to numerous cardiac specific promoters, the knowledge concerning IRES and angiogenic factors, the specific arrangement falls within the bound of optimization of an expression cassette. It

is also noted if the genus is to be examined as currently claimed generically, even less supplemental references are required.

Applicants then argue that they have previously explained that the invention as claimed provides some results that is production of a pure or very nearly pure culture of cells that express the physiologic properties of cardiomyocytes, that is unexpected in view of the cited references. Applicants allege that the Examiner dismisses Applicant's argument about the unexpected results on the grounds that the claims are not limited by the physiological properties of the cells, but such properties are not necessary to recite in the claims.

In response, as an initial matter, it is noted that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. MPEP 716.01(c). Therefore, the assertion needs to be supported by an appropriate affidavit or declaration detailing in what aspect the claimed invention is unexpected.

Further, the rebuttal for the asserted unexpected results is based on the teaching of the cited references as analyzed in detail in the previous Office action (pages 18-19), and the assertion is not dismissed by the limitation of the produced cells. Particularly noteworthy is the fact that *Klug et al* clearly teach that the selection for a particular

subtype of cardiac cells (ventricular or atrial) is a matter of refinement, and could be achieved by selecting for a particular promoter (page 222, 3rd paragraph), and they have shown that MLC-2v (as used by applicants) would select for ventricular cardiac cells (fig. 3, top panel). As to the purity of the selected population, *Griscelli et al* teach that three rounds of magnetic cell sorting yield > 90% CD4+ cell population (abstract), and *Klug et al* obtained a cardiomyocyte population with >99% purity (e.g. last paragraph, left column, page 222), thus, it does not appear anything taught by applicants is unexpected, particularly considering the current claims are drawn to a genus of cassettes using various combinations of promoters and enhancers, each is selected from a genus, which encompasses the combination taught by the combined teachings of *Klug et al, Gaines et al, Griscelli et al, Wolfgang-M et al, in view of Mack et al* .

Accordingly, the combined teachings of the cited art meet each and every limitation of the claims, and the claimed invention is obvious over combined teachings of cited prior art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Q. Janice Li
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QJL
October 15, 2004